

REMARKS

Claims 3-5 and 8-11 remain pending in this application, with claim 3 being the only independent claim.

New Matter Rejection

The Advisory Action indicated that the June 23 Amendment, which was entered, overcame the indefiniteness rejections and enablement rejections of the Final Rejection, but that claim 3 introduced new matter based on a new last step: "reducing said product to form the compound of formula Ib." Applicants understand that the indication that this prior amendment of claim 3 as introducing new matter means that such amendment requires the Examiner's new consideration of an issue after final rejection, rather than the amended language is new matter not supported by the application under 35 U.S.C. § 132(a), last sentence. The Examiner himself pointed out in item 6 of the Final Rejection that a reduction step was set forth in the paragraph bridging pages 11 and 12. The reduction step is also exemplified in Example 7, resulting in a product within the definition of formula Ib.

Since this Request for Consideration accompanies an RCE, including the payment of the RCE fee, it is believed that the introduction of new matter issue raised in the Advisory Action is now moot.

Claim Rejections Under 35 U.S.C. § 103(a)

The Final Rejection rejected the original claims under 35 U.S.C. § 103(a) as being anticipated by Yan in view of House, both of record. The Advisory Action referred to a Declaration of Harry Kochat, one of the inventors and the Head, Chemistry Drug Discovery and Senior Manager of CMC Operations of BioNumerik Pharmaceuticals, Inc., the assignee of this invention and application, that was filed with the June 23 Amendment (the "first Kochat Rule 132 Declaration"). The Advisory Action concluded that the first Kochat Rule 132 Declaration was not convincing of the patentability of the invention. The Advisory Action indicated that the first Kochat Rule 132 Declaration compared apples with oranges relating to an attempt to show an increased yield, because the products that were prepared by different methods in the first Kochat Rule 132 Declaration were not the same products. The Advisory Action also noted that the product including the yield data was a carbomethoxy compound where X is OCH₃, but the

claimed scope of X is broader, such that the evidence is not commensurate in scope with the claims. The Advisory Action further indicated that a yield increase from 73% to 83% is a change in degree, not a change in kind. Additionally, it was indicated that triphenylphosphine oxide is notorious for being bulky, difficult to remove, and for appearing in every chromatographic fraction, and thus, the easier workup in a process which does not involve this by-product is hardly unexpected. The final indication in the Advisory Action is that the two reactions presented in the first Kochat Rule 132 Declaration are based on results from the literature where the source of the data was not identified.

This request for reconsideration, together with an accompanying Supplemental Declaration of Harry Kochat, Ph.D. Under 37 C.F.R. § 1.132 (the "Kochat Supplemental Declaration"), addresses each of the foregoing issues. Reconsideration and withdrawal of the obviousness rejections in the Final Rejection, as repeated or modified in the Advisory Action, are respectfully solicited in view of the Kochat Supplemental Declaration and the following explanations.

The Kochat Supplemental Declaration, in paragraphs 2 and 3, presents different reactions to make the same product, resulting in significantly different yields. As noted in paragraphs 2 and 3 of the Kochat Supplemental Declaration, the reactions and procedures both relate to the same compound, the unsaturated precursor compound to the formula Ib compound as claimed, and as shown in Example 6 of the application. The workups in the Kochat Supplemental Declaration thus compare apples to apples and confirm that a yield of 86% was achieved using the modified Wittig-Horner reaction as shown in paragraph 2 and in Examples 5 and 6 of the application. This is compared to a 72.8% estimated yield based on HPLC peak areas while producing the same product using the standard Wittig reaction as shown in paragraph 3 of the Kochat Supplemental Declaration.

The Advisory Action included a position that an increase in yield from 73% to 83% is not a significant increase (a change in degree, not a change in kind). Applicants respectfully disagree. In fact, an increase even of 10% yield, let alone 13% yield as achieved in the present case, is a very significant increase in yield from a commercial viewpoint. The reasons are set forth in the Kochat Supplemental Declaration paragraph 7.

Although Examples 5 and 6 in the application and paragraph 2 of the Kochat Supplemental Declaration provide data relating to a compound where X is OCH₃, Dr. Kochat

explained in paragraph 4 of the Kochat Supplemental Declaration that the low yield seen for this compound was also seen in other compounds prepared at BioNumerik, though such other compounds were not necessarily within Formula Ib. Nevertheless, based on his experience and the data provided in the Kochat Supplemental Declaration, low yield for the compounds claimed in this application if made by a Wittig reaction would be expected, and, based on the data provided with respect to the modified Wittig-Horner reaction, an improved yield would be expected for such Formula Ib compounds and their unsaturated precursors.

Ultimately, the Advisory Action concluded that the workup of the Horner reaction shown in the House reference would hardly be unexpected to avoid the asserted "notorious" problems associated with the triphenylphosphine oxide process shown in Yan, rendering the presently claimed invention not patentable as being obvious over the combination of Yan and House. Applicants respectfully but strenuously traverse this rejection.

It is important to note that the compounds with which the claimed process is involved include pteridine compounds or quinazoline compounds. With reference for instance to Examples 5 and 6 of the application and paragraph 2 of the Kochat Supplemental Declaration, the 2,4-diamino-quinazoline-6-carbaldehyde includes two unprotected amino groups which may be expected to react in a manner detrimental to the formation of the desired product, an unsaturated precursor to the Formula Ib compound. These types of starting materials were not shown or described in House which used a modified Wittig-Horner reaction for different types of compounds. To assure the formation of the desired unsaturated intermediate, also not disclosed in House, the prior art as represented by the Wittig reaction shown in paragraph 3 of the Kochat Supplemental Declaration used the Wittig reaction including the triphenylphosphine moiety in the presence of the strong organic base potassium t-butoxide. The organic base was needed to assure the formation of the unsaturated bond in favor of a reaction with the unprotected amino groups.

By using the modified Wittig-Horner reaction, not only was the yield increased significantly, as mentioned above, due to avoidance of the formation of triphenylphosphine oxide which would then have to be removed, but could not be, but also the Wittig-Horner reagent itself had sufficient basicity to avoid having to use any separate organic base to produce the unsaturated intermediate shown in Example 6 and in the second reaction of paragraph 2 of the Kochat Supplemental Declaration. This was a surprising result that was not expected based on

the prior art Wittig reaction or even based on House, since House was not involved with reacting compounds having unprotected amino groups, such as pteridine or quinazoline compounds. See the Kochat Supplemental Declaration paragraphs 5 and 6.

As also set forth in the Kochat Supplemental Declaration paragraph 5, even assuming only for the sake of argument that problems of the prior art Wittig reaction of the type shown in Yan were well known and were to be avoided, overcoming the problems was not an easy solution in the present case. The House reference notwithstanding, if a Wittig-Horner reaction were known with respect to compounds including a pteridine or quinazoline moiety, one would have expected them to be reported in the literature, though research failed to reveal any such reactions. Even BioNumerik's contract manufacturers, who are charged with making commercial products efficiently, did not realize or develop the idea of using a modified Wittig-Horner reaction to produce the claimed compounds or their unsaturated precursors.

Even further, it would not have been obvious to substitute the modified Wittig-Horner reaction of House for the Wittig reaction of Yan because neither Yan nor House revealed a suitable commercially scalable process. For example, Yan discloses in the middle paragraph in the left column of page 542 that the Wittig condensation of compounds VIe and VIIIb was carried out by stirring the phosphonium bromide VIIIb in sodium hydride in dimethylformamide followed by the addition of VIe. The reaction was completed in four days at room temperature to form IX, which was hydrogenated catalytically to give compound X. A process that takes four days to proceed as disclosed in Yan is not a commercially viable process, even if the adverse by-product formation could be reduced or eliminated, which it could not.

The reactions proposed by House do not appear to be appropriately commercially scalable either. The Advisory Action referred to a chromatographic separation or isolation procedure. However, a chromatographic isolation procedure is not a practical commercial process, as explained in paragraph 6 of the Kochat Supplemental Declaration, due to a huge amount of chromatographic adsorbent or solid support that would be needed, together with a huge amount of solvent that would be needed to elute the product.

In summary, there was a lack of guidance provided by the prior art literature and lack of guidance provided by commercial manufacturers involved in the preparation of the desired pteridine or quinazoline compounds to even suggest the use of a modified Wittig-Horner reactant to produce such compounds or their unsaturated precursors. Moreover, there was no recognition

in the prior art of the dual functionality of the modified Wittig-Horner reaction both to produce the coupling of the desired reactants including the unprotected amino groups, while eliminating the need for a separate organic base in the reaction to assure formation of the desired unsaturated pteridine or quinazoline compounds. In view of the evidence presented in the Kochat Supplemental Declaration and the distinctions resulting from the unprotected amino group, a person of ordinary skill in the art, without the benefit of the hindsight provided by the present application, would not have used the modified Wittig-Horner reaction to produce such compounds involving the pteridine or quinazoline moieties.

Reconsideration and withdrawal of all of the rejections and an early Notice of Allowance are respectfully solicited.

Respectfully submitted,

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(Date)

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